TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35.U.S.C. 371

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INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IT97/00040	27 February 1997	28 February 1996

TITLE OF INVENTION
PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON

APPLICANT(S) FOR DO/EO/US 1-a Giulio Tarro and 2-a Renato Brozzo

Applicant herewith submits to the United States Designated /Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [x] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [x] Other items or information:
    A copy of the specification and claims
    PCT Demand
    International Search Report
    Notification of Transmittal of International Preliminary Examination Report

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB97/00040	27 FEBRUARY 1997	28 FEBRUARY 1996

17. [x] The following fees are submitted:

CALCULATIONS PTO USE ONLY

Basic National Fee (37 CFR 1.492(a)(1)-(5):

Search Report has been prepared by the EPO or JPO $930.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) $720.00

No international preliminary examination fee paid to USTPO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $790.00

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1,070.00

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... $ 98.00

ENTER APPROPRIATE BASIC FEE AMOUNT =	$930.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] **20** [ ] **30** months from the earliest claimed priority date (37 C.F.R. 1.492(e)).	$	

Claims	**Number Filed**	**Number Extra**	**Rate**	$	
Total Claims	8 -20=	-0-	X $ 22.00	$-0-	
Independent Claims	3 -3=	-0-	X $ 82.00	$-0-	
Multiple dependent claim(s) (if applicable)			+ $270.00	$ 270.00	
TOTAL OF ABOVE CALCULATIONS =				$1200.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$1200.00	
Processing fee of $130.00 for furnishing the English translation later than [ ] **20** [ ] **30** months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$1200.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$1200.00	
				Amt.refunded	$
				charged	$

a. [x] A check in the amount of $ 1200.00 to cover the above fees is enclosed.

b. [ ] Please charge our Deposit Account No. 02-4377 in amount of $___ to cover the above fees. A copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4377. A copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BAKER & BOTTS, L.L.P.
30 Rockefeller Plaza
New York, New York 10112-0228

Signature Ronald B. Hildreth

August 10, 1998
Date

19,498
Registration No.

PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON

The invention concerns pharmaceutical compositions for a peroral administration comprising natural human α-interferon isolated from lymphoblastoid or leukocitic cells. In particular compositions are useful for therapy of viral infections, in particular viral hepatitis, neoplasia and immunodeficiency syndromes. The interferon efficient dosages are clearly lower than dosages utilized for parenteral administration.

α-, β-, γ-interferons are usually administered by injection and are used for therapy. α-interferon is the most largely utilized interferon (1). In an updated study of medicaments for either acute or chronic viral hepatitis therapy (2), only α-interferon is widely accepted as single therapeutic agent.

"Viral hepatitis" means at least five different pathologies, having different agents, namely A, B, C, D, E.

The therapeutic trend is to treat said pathologies with α-interferon, with dosages according to the kind of hepatitis, to the overall status of the subject and to other variable factors. In general, further to the interferon treatment an almost normalisation clinical and biochemical parameters is achieved for chronic hepatitis (B, C, D). The interferon activity on acute hepatitis has not been focused yet, though for hepatitis C, a therapeutic treatment with α-interferon lowers the chronicition rate of the disease.

Therapeutic cycles indicate the day alternate administration through subcutaneous route of recombinant α-interferon (r α-IFN) at dosages of app. 5.000.000 UI, that in special cases can be up to 9.000.000 UI/day.

The length of therapeutic cycles is of from six months up to one year (nine months average).

In many cases, undesired side effects interfere with the course of therapeutic treatment. In fact some patients, in particular those at an advanced stage of disease or with severe physiologic damages, do not tolerate the therapy and therefore the treatment should be interrupted. Claimed side effects are: fever, nausea, vomit, tiredness, algia and depression.

Moreover the therapeutic cost are quite relevant both due to the high amount of active principle (more than 8.000 new cases each year in Italy and 300.000 world-wide) and to the necessity of hospitalisation just in consideration of said side effects further to the parenteral administration (day hospital or outpatients' department).

Finally, as far as chronic active viral hepatitis the only alternative to the interferon treatment is represented by liver transplant.

The clinical trend is to increase the posology dosage and the length of therapeutic cycle (3), but clinical data show (4): severe side effects; low acceptance by the patient; high therapeutic costs. Garcia et al. (5) report that the estimate for each cured patient is between 700.000 and 2.000.000 English pounds Capri S. (6) report that the cost of each interferon therapeutic treatment is of Lit. 70.000.000/subject.

It is therefore evident that the actual composition of interferon for therapeutic treatment of hepatitis is not optimal.

Moreover clinical results show a better therapeutic efficacy in patients which are not the main target for therapy, namely: young subjects, subjects with a disease at an initial stage, subjects infected with genotipic virus 2 or 3, low viremia subjects. On the contrary a less therapeutic efficacy can be found in those subjects which really need the therapeutic treatment (subjects poco respondent), as subjects affected by an aggressive

form (active chronic hepatitis), long length diseases affected subjects, over 50 subjects. Thus patients that really need an immediate interferon treatment are those that have a lower chance of success (7).

The authors of the instant invention have found a pharmaceutical composition comprising natural human α-interferon from either lymphoblastoid or leukocitic cells to be administered through peroral route, with dosages clearly lower than those used for parenteral administration. The composition maintains as unaltered chemical-physical, biological and pharmacological characteristics of the active principle, having a therapeutic effect substantially analogous to the compositions of prior art but overcoming disadvantages thereof.

The composition is preferably in a liquid form with a concentration of 100 to 500 UI/ml, preferably approx. 150 UI/ml, most preferably in mono-dosage units, most preferably of appr. 1 ml.

The composition acts by activating the defence mechanisms against viral infections, tumour growth and stimulates an immune response.

The utilisation of natural interferon was chosen for the better chances of therapeutic success with respects to recombinant interferon, obtained by cloning of a single subtype.

Though leukocitic and lymphoblastoid interferons exert the same therapeutic properties, the former can be advantageously produced. As a matter of fact it is obtainable by stabilised cell lines, without the need of blood donors.

Processes for purifying interferons are known to those skilled in the art, and for example are shown in US Patent 4,732,683; in Cantell K. and Hirvonen S. Texas Reports on Biology and Medicine, Vol. 35, p.138, 1977; in Zoon K.C. et al. Science 207, p. 527, 1980.

The peroral route is generally much more accepted by subjects, makes easier posology schemes and dosages, lowers to stops the antigenic risk, induces the transmission and amplification signal mechanism, with a mirato therapeutic effect, with dosages 100 times lower than known formulations for parenteral administrations.

The low dosage annuls the risk of toxic effects; allows a better availability of medicine to satisfy an increasing request and a drastic lowering of therapeutic costs.

The preferred formulation in dosage units of small volumes (1 ml) to drink allows an immediate availability of the active principle, a good standard of cleanliness from the monodosage primary container; the certainty of the taken dosage; the taking of the active principle to be immediately adsorbed by the oro-pharyngeal mucosa, easily preventing the deglutition, an ease and safe way of administration for all of patients, as opposite to lozenges or tablets formulations that should be kept in the mouth till to full dissolution, with high chances of swallowing.

Moreover the composition of the invention is conveniently used for home therapies or on the job place, as precautionary measure for the prophylaxis of viral pathologies, and to control chronic diseases which need of long therapeutic cycles (even yearly) and often recurrent.

The composition can be used also in association with other drugs to get synergism and optimize therapeutic schemes.

The following clinical studies show the therapeutic effect. A comparison of the electrophoretic protein pattern and of the concentration of IgG, IgA, IgM, before the beginning of the peroral therapy with natural human α-interferon of hepatitis or other pathologies affected subjects, before and after two weeks of therapeutic

treatment, allows to foreseen quali-quantitatively the subject response.

Subjects which respond to the therapy with 450UI/die dosages show a decrease of α2- and ß-globulins, of IgGs, of the IgG/IgA ratio, together to an increase of IgA and IgM concentrations, have a good chance of eliminate the HBVe antigen and to seroconvert, namely to confer a stable remission of the pathology.

On the other hand subjects which respond to the same therapy with a decrease of albumin serum concentration, of IgGs, IgAs, IgMs, together to an increase of α1-globulin fractions, should seronvert with longer times.

Moreover subjects that respond with an increase of IgGs, of the IgG/IgA ratio, together to a decrease of IgM and of the IgA/IgM ration, could be resistant to the therapy.

The monitoring of said parameters (markers) is useful for a planning of therapeutic strategies in clinic and also for the clinical practitioner.

Clinical studies on healthy subjects

Table 1 shows different therapeutic schemes.

Table 1

Exp.		active comp.	No. admin. /day	Dosages	days trt.	blood bleedings
A	aA	α-IF	1(3dsg)	450 UI	1	$T_0, T_1, T_2, T_3,$
	aB	placebo	1(3dsg)	-	1	T_0, T_1, T_2, T_3
B	bA	α-IF	1(3dsg)	450 UI	5	$T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7$
	bB	placebo	1(3dsg)	-	5	$T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7$
C	cA_1	α-IF	2(1dsg)	300 UI	1	T_0, T_1, T_2, T_3
	cA_2	α-IF	3(1dsg)	450 UI	1	T_0, T_1, T_2, T_3
	cb	placebo	3(1dsg)	-	1	T_0, T_1, T_2, T_3
D	dA_1	α-IF	2(1dsg)	300 UI	5	$T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7$
	dA_2	α-IF	3(1dsg)	450 UI	5	$T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7$
	dB	placebo	3(1dsg)	-	5	$T_0, T_1, T_2, T_3, T_4, T_5, T_6, T_7$

T_0 = background; T_1 = 1d further the first administration, T_2 = 2d further the first administration, T_3 = 3d further the first administration, T_4 = 4d further the first administration, T_5 = 5d further the first administration, T_6 = 1d after the treatment suspension, T_7 = 2d after the treatment suspension.

The change of the induced biological response with respect to the therapeutic scheme, has been measured on samples of blood, taken at different times. In particular the activity with respect to the day dosage of active principle, to the mono- or pluri-administration, to the length of the therapeutic cycle was measured.

The analysis of data show that natural human α-interferon from either lymphoblastoid or leukocitic cells, administered at low dosages for a peroral route, is able to modulate (according to the dosage and to the length of the therapeutic cycle) the expression of membrane antigen of healthy subject blood mononuclear cells. In particular, according to therapeutic scheme, the pharmaceutical composition seems to be able to increase both CD4 and CD8 cell population. It is also evident an increased expression of markers of cell activation, as DR antigens and interleukin 2 receptor.

The therapeutic scheme with 450 U/die x 5 d (exp.b) is the one provided better results, as shown in Tables 2 and 3. In fact there is an increase (% and absolute) of CD3, CD4, DR1, CD25 lymphocytes. Said increases are, according to different cases, better evident at T_3, T_4, T_5 times to later decrease at T_6 and T_7 times.

The same posology dosage, but with a shorter therapeutic cycle (1 day) (exp.a), interferes less evidently with the % and absolute numbers of mononuclear cells in the blood (Tables 4 e 5). In fact in this experiment an increase of average percentage values but not of absolute T, CD8, and class II hystocompatibility antigen lymphocytes values, is evident at time T_3.

Other experimental conditions show lower increases of the immune response.

Therefore, natural human α-interferon from either lymphoblastoid or leukocitic cells, administered at low dosages trough peroral route, shows an important role in modulating the immune response, both in the phase afferent than efferent, e has a therapeutic application for the treatment of infective diseases and of other conditions of immunodeficiency.

Clinical studies on hepatitis subjects

Viral B Hepatitis

14 patients affected by chronic viral B hepatitis, with an age comprised between 4 and 59, were used for random studies.

All of subject were previously treated for different periods ranging from some months to some years with steroids, or with steroid-azothiopurine, with no beneficial effects, neither for the clinical symptomatology nor for the biochemical parameters of the disease, which evolved, in some cases, to hepatic cirrhosis.

The therapeutic treatment of a one administration of 150U/day was initiated immediately after the suspension of the previous treatment, and effects of said treatment were monitored by checking any alteration of the immune response; of the haematological and biochemical parameters; of serum markers of the viral infection and of the hystochemistry of hepatic bioptic samples.

The time of observation varied from 15 to 32 months and results can be summarized in the following:

1) all of patients during the first 3-6 weeks of treatment registered a transient decay of hepatic biochemical functions (i.e. a 2-3 fold increase of alanineaminetransferase (ALT) levels), with no clinical symptoms of disease worsening;

2) the phenomenon goes on for 4-6 weeks;

3) in all of treated patients an intense activation of the immune system was observed, even after the therapeutic treatment;

4) 7 patients eliminate HBV DNA and HBeAg from serum and stable seroconvert;

5) 1 patient has an HBcAg increased title, more than the original value;

6) in other 9 patients said titre decreases significatively.

Therefore, 50% of patients get a stable remission of the disease.

Viral C Hepatitis

The therapeutic standard of viral hepatitis C foresees the use of α-interferon through parenteral route.

6 active chronic hepatitis C affected patients were subjected to therapy with peroral administration at 150U/die, by starting the treatment just after the suspension of the steroid therapy.

The observation time (equal to the length of the treatment) resulted to be variable from 19 to 69 weeks. In general the treatment was well tolerated and all of patients registered a significant increase of vivacity and appetite, with a better tolerance to physical exercises.

No patients got a normalization of transaminase levels during the observation period, but one which registered the biochemical and clinical remission of the disease, after the treatment suspension at the 19th week due to an increasing of articular pains.

Results are shown in tables 2-5.

BIBLIOGRAPHY

1) Howard M. et al. Le Scienze n.311 Vol LIII 72-80 (1994).

2) Saracco G., Rizzetto M. Biomed. Pharmacother. 49 (2),55-57 (1995).

3) Kasahara A.K., et al., Hepatology; 21, 291-297 (1995).

4) Paoletti A. et al.; Clin. Ter. 146(5), 343-349 (1995).

5) Garcia De Ancos J.L. et al.; J. Hepatol. 11:s11-s18 (1990).

6) Capri S. Adis International, Milano, pp 41-49 (1994).

7) Bianchi F.B., La rivista del medico pratico, Ott. (suppl.5) (1995).

TREATMENT	TIME	%CD3	%CD4	%CD8	%CD25	%MHCII	%B	%NK	%CD14
450UI/d x 5d 3ds	T_0	69,2±4,9	42,8±4,3	26,3±2,9	1,4±0,9	7,5±0,8	11,5±1,1	6,9±0,7	10,3±1,6
PLACEBO x 5d 3ds	T_0	71,3±5,2	41,7±4,1	24,5±3,5	<0,5	8,1±1,2	13,1±1,6	8,1±1,3	9,3±1,2
450UI/d x 5d 3ds	T_1	70,1±5,1	43,1±4,5	25,8±3,1	<0,5	8,2±1,3	12,1±1,4	7,2±1,3	3,9±1,4
PLACEBO x 5d 3ds	T_1	72,4±5,4	40,8±3,9	25,3±3,8	<0,5	8,7±1,4	12,7±1,8	8,2±1,5	10,1±1,3
450UI/d x 5d 3ds	T_2	70,2±5,1	44,2±3,1	23,2±3,1	1,7±1,3	9,1±1,3	12,5±1,6	7,1±0,9	11,1±1,5
PLACEBO x 5d 3ds	T_2	70,8±5,3	41,1±4,2	24,7±3,7	1,2±0,9	8,7±1,4	11,4±1,6	6,9±1,9	10,8±1,7
450UI/d x 5d 3ds	T_3	69,8±5,7	49,4±4,9	24,1±3,6	2,5±1,6	14,2±1,3	12,1±1,4	7,2±1,1	9,7±1,8
PLACEBO x 5d 3ds	T_3	71,3±5,6	41,5±4,3	24,4±3,5	<0,5	8,5±1,3	13,1±1,8	6,9±1,7	10,1±1,8
450UI/d x 5d 3ds	T_4	72,3±5,8	49,7±5,1	23,8±3,8	2,3±1,7	14,2±2,5	12,5±1,8	6,8±0,9	9,4±1,5
PLACEBO x 5d 3ds	T_4	69,8±5,3	40,9±4,2	25,2±4,3	<0,5	7,9±0,9	12,9±1,9	7,1±0,7	11,6±2,1
450UI/d x 5d 3ds	T_5	71,8±5,4	53,3±4,9	74,2±4,1	2,5±1,6	14,2±1,9	13,5±2,1	7,3±0,9	11,3±1,6
PLACEBO x 5d 3ds	T_5	70,6±5,5	41,3±4,1	25,9±4,4	1,4±1,3	8,1±1,3	12,6±1,4	7,5±0,9	9,9±2,3
450UI/d x 5d 3ds	T_6	69,7±5,2	50,7±4,7	23,7±4,1	1,6±0,9	11,3±1,5	12,8±1,9	6,9±0,6	10,8±1,9
PLACEBO x 5d 3ds	T_6	71,3±5,6	42,3±4,3	24,7±3,8	<0,5	7,9±1,4	11,4±1,1	7,3±0,5	10,4±1,9
450UI/d x 5d 3ds	T_7	70,2±5,1	45,3±4,4	24,2±3,8	1,1±0,9	8,7±1,1	12,3±1,6	7,1±0,7	11,2±7,1
PLACEBO x 5d 3ds	T_7	71,5±5,8	41,5±3,9	25,1±4,1	<0,5	8,1±1,6	11,9±1,4	7,8±0,8	9,8±1,7

b vs a = $p<0,05$; c vs a = $p<0,01$; e vs d = $p<0,01$; f vs d = $p<0,05$ Student's "t" test

Tab. 2 -

TREATMENT	TIME	CD3 n°/mm³	CD4 n°/mm³	CD8 n°/mm³	CD25 n°/mm³	MHCII n°/mm³	B n°/mm³	NK n°/mm³	CD14 n°/mm³
450UI/d x 5d 3ds	T_0	1776±323	1074±208	560±145	35±23	186±60	288±87	173±68	177±78
PLACEBO x 5d 3ds	T_0	1658±220	970±195	565±171	<13	188±68	305±77	188±90	203±88
450UI/d x 5d 3ds	T_1	1858±126	1142±213	684±95	<13	217±53	320±65	191±73	213±95
PLACEBO x 5d 3ds	T_1	1784±195	1005±191	623±182	<13	214±73	313±142	302±85	216±90
450UI/d x 5d 3ds	T_2	1986±130	1251±115	657±98	48±33	258±43	354±70	301±73	196±138
PLACEBO x 5d 3ds	T_2	1746±183	1034±197	594±182	30±20	215±103	281±87	170±84	205±140
450UI/d x 5d 3ds	T_3	1878±132	1339±223	648±190	67±40	382±65	326±65	194±78	243±75
PLACEBO x 5d 3ds	T_3	1555±190	905±230	530±81	<11	185±130	286±52	150±99	234±72
450UI/die x 5d 3ds	T_4	1994±178	1325±168	539±195	62±43	381±90	336±145	183±75	187±48
PLACEBO x 5d 3ds	T_4	1733±213	1138±197	701±200	<14	230±121	359±174	198±76	167±69
450UI/d x 5d 3ds	T_5	2001±175	1456±283	579±203	70±40	399±108	379±88	205±73	197±140
PLACEBO x 5d 3ds	T_5	1720±226	1007±195	531±132	34±31	197±115	307±153	183±71	196±131
450UI/d x 5d 3ds	T_6	1719±170	1238±175	585±170	39±23	379±138	316±84	170±75	213±68
PLACEBO x 5d 3ds	T_6	1578±230	736±300	547±138	<11	175±132	252±126	162±62	242±74
450UI/d x 5d 3ds	T_7	1704±128	1058±170	586±105	27±23	211±128	298±97	172±78	197±83
PLACEBO x 5d 3ds	T_7	1595±235	924±191	559±195	<11	180±51	265±133	174±65	228±90

b vs s = p<0,05 ; d vs c = p<0,05 ; f vs c = p<0,01 Student's "t" test

Tab. 3 =

TREATMENT	TIME	%CD3	%CD4	%CD8	%CD25	%MHCII	%B	%NK	%CD14
450UI/d x 1d 3ds	T_0	70,3±5,7	42,4±3,8	25,3±2,6	1,7±1,4	7,2±0,8	9,7±1,4	8,4±0,9	8,4±0,7
PLACEBO x 1d 3ds	T_0	69,9±5,3	43,8±4,2	24,3±2,7	<0,5	7,9±0,9	10,9±1,7	7,8±0,8	9,8±0,9
450UI/d x 1d 3ds	T_1	69,4±5,5	43,9±4,5	24,8±1,9	<0,5	8,3±1,3	10,5±1,7	9,3±2,1	8,3±0,8
PLACEBO x 1d 3ds	T_1	70,2±5,9	43,5±4,4	23,8±2,5	<0,5	8,2±1,3	11,2±1,8	7,3±1,2	8,5±0,6
450UI/d x 1d 3ds	T_2	73,6±6,1	43,5±4,3	27,3±3,1	<0,5	8,1±1,2	11,2±2,1	10,7±4,5	9,3±1,5
PLACEBO x 1d 3ds	T_2	70,1±5,6	44,1±4,7	24,7±3,1	1,4±0,9	7,7±1,4	12,1±2,7	6,1±0,9	8,8±1,3
450UI/d x 1d 3ds	T_3	77,8±6,2	44,1±4,8	2,7±2,4	2,3±1,9	11,2±1,5	10,9±1,9	8,3±0,7	12,2±3,1
PLACEBO x 1d 3ds	T_3	70,3±5,4	43,9±5,1	24,7±3,3	<0,5	8,1±0,9	10,5±1,7	8,5±1,6	10,7±1,4

b vs a = $p<0,01$; c vs d = $p<0,05$; e vs f = $p<0,05$ Student's "t" test

Tab. 4 =

TREATMENT	TIME	CD3 n°/mm³	CD4 n°/mm³	CD8 n°/mm³	CD25 n°/mm³	MHCII n°/mm³	B n°/mm³	NK n°/mm³	CD14 n°/mm³
450UI/d x 1d 3ds	T_0	1521±223	917±182	547±156	37±30	156±77	210±80	182±80	182±75
PLACEBO x 1d 3ds	T_0	1615±222	1012±197	561±162	<12	183±81	252±99	180±86	210±81
450UI/d x 1d 3ds	T_1	1501±218	949±189	536±141	<11	180±128	227±97	201±57	192±79
PLACEBO x 1d 3ds	T_1	1637±236	1014±202	555±188	<12	191±80	261±72	170±89	177±63
450UI/d x 1d 3ds	T_2	1587±132	938±183	589±97	<11	175±126	242±85	230±98	215±72
PLACEBO x 1d 3ds	T_2	1723±329	1083±189	607±172	34±21	189±82	297±62	199±71	206±80
450UI/d x 1d 3ds	T_3	1654±234	940±184	631±101	49±41	238±124	231±91	176±76	234±67
PLACEBO x 1d 3ds	T_3	1673±124	1045±178	588±76	<12	193±91	250±49	202±94	251±82

b vs a = $p<0,05$; d vs c = $p<0,05$; f vs e = $p<0,01$ Student's "t" test

Tab. 5 =

CLAIMS

1. Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of viral hepatitis in humans and animals.

2. Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of neoplasia and immunologic diseases in humans and animals.

3. Use of natural human α-interferon according to claims 1 or 2 wherein said interferon is obtained from lymphoblastoid cell cultures.

4. Use of natural human α-interferon according to claims 1 or 2 wherein said interferon is obtained from lymphocyte cells.

5. Use of natural human α-interferon according to any of previous claims wherein said medicament is administered in mono dosage units of appr. 1 ml.

6. Pharmaceutical liquid composition for peroral administration comprising natural human α-interferon either from lymphoblastoid cell cultures or from lymphocyte cells at a concentration between 100 UI/ml and 500 UI/ml.

PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON

Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of viral infections, in particular viral hepatitis, neoplasia and immune diseases in humans and animals.

COMBINED DECLARATION AND POWER OF ATTORNEY

(Original, Design, National Stage of PCT, Divisional, Continuation or C-I-P Application)

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON"
This declaration is of the following type:

[] original
[] design
[X] International stage of PCT.
[] divisional
[] continuation
[] continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b), or (c))*

(a) [ ] is attached hereto.
(b) [X] was filed on August 11, 1998 as Application Serial No. 09/125,122 and was amended on *(if applicable).*
(c) [X] was described and claimed in PCT International Application No. PCT/IT97/00040 filed on FEBRUARY 27, 1997 and was amended on *(if applicable).*

Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

[ ] In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [X] such applications have been filed as follows:

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION				
COUNTRY	APPLICATION NO.	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
ITALY	RM96A000136	28-2-96		[X] YES NO []
				[] YES NO []
				[] YES NO []
ALL FOREIGN APPLICATION[S], IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION				
				[] YES NO []
				[] YES NO []
				[] YES NO []

Claim for Benefit of Prior U.S. Provisional Application(s)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Provisional Application Number	Filing Date

Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120

(complete this part only if this is a divisional, continuation or C-I-P application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

Power of Attorney

As a named inventor, I hereby appoint Dana M. Raymond, Reg. No. 18,540; Frederick C. Carver, Reg. No. 17,021; Francis J. Hone, Reg. No. 18,662; Joseph D. Garon, Reg. No. 20,420; Arthur S. Tenser, Reg. No. 18,839; Ronald B. Hildreth, Reg. No. 19,498; Thomas R. Nesbitt, Jr., Reg. No. 22,075; Robert Neuner, Reg. No. 24,316; Richard G. Berkley, Reg. No. 25,465; Richard S. Clark, Reg. No. 26,154; Bradley B. Geist, Reg. No. 27,551; James J. Maune, Reg. No. 26,946; John D. Murnane, Reg. No. 29,836, Henry Tang, Reg. No. 29,705, Robert C. Scheinfeld, Reg. No. 31,300, John A. Fogarty, Jr., Reg. No. 22,348, Louis S. Sorell, Reg. No. 32,439 and Rochelle K. Seide Reg. No. 32,300 of the firm of BAKER & BOTTS, L.L.P., with offices at 30 Rockefeller Plaza, New York, New York 10112, as attorney s to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith

SEND CORRESPONDENCE TO:	DIRECT TELEPHONE CALLS TO:
BAKER & BOTTS, L.L.P. 30 ROCKEFELLER PLAZA, NEW YORK, N.Y. 10112 CUSTOMER NUMBER: 21003	BAKER & BOTTS, L.L.P. (212) 705-5000

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF SOLE OR FIRST INVENTOR: 1-00	LAST NAME: TARRO	FIRST NAME: GIULIO	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY: ROME	STATE or FOREIGN COUNTRY: ITALY	COUNTRY OF CITIZENSHIP: ITALY ITX	
POST OFFICE ADDRESS	POST OFFICE ADDRESS: VIA PAOLO FRISI, 21/23	CITY: ROME	STATE or COUNTRY: ITALY	ZIP CODE: I-00197
DATE	SIGNATURE OF INVENTOR: [signature]			
FULL NAME OF SECOND JOINT INVENTOR, IF ANY 2-00	LAST NAME: BROZZO	FIRST NAME: RENZO	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY: ROME	STATE or FOREIGN COUNTRY: ITALY	COUNTRY OF CITIZENSHIP: ITALY ITX	
POST OFFICE ADDRESS	POST OFFICE ADDRESS: VIA PAOLO FRISI, 21/23	CITY: ROME	STATE or COUNTRY: ITALY	ZIP CODE: I-00197
DATE	SIGNATURE OF INVENTOR: Renzo Brozzo			
FULL NAME OF THIRD JOINT INVENTOR, IF ANY	LAST NAME:	FIRST NAME:	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY:	STATE or FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE or COUNTRY:	ZIP CODE:
DATE	SIGNATURE OF INVENTOR:			
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY	LAST NAME:	FIRST NAME:	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY:	STATE or FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE or COUNTRY:	ZIP CODE:
DATE	SIGNATURE OF INVENTOR:			
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	LAST NAME:	FIRST NAME:	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY:	STATE or FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE or COUNTRY:	ZIP CODE:
DATE	SIGNATURE OF INVENTOR:			
FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	LAST NAME:	FIRST NAME:	MIDDLE NAME:	
RESIDENCE & CITIZENSHIP	CITY:	STATE or FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:	
POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE or COUNTRY:	ZIP CODE:
DATE	SIGNATURE OF INVENTOR:			